Nicholas E. S. Sibinga, M.D., above, wants to prevent two of America’s leading killers: heart attacks and strokes. Key risk factors for both are high blood pressure and high blood cholesterol, and Dr. Sibinga’s strategy is to minimize the blood vessel damage they cause.

Dr. Sibinga, an associate professor of medicine (cardiology) and of developmental and molecular biology, studies the earliest effects of high blood pressure and high cholesterol at the molecular level.

High blood pressure and high blood cholesterol affect arteries differently. The damage from high blood pressure starts as inflammation that can lead to hardened, thickened, inflexible arteries (arteriosclerosis); high blood cholesterol leads to artery-clogging fat buildup (atherosclerosis).

Dr. Sibinga focuses on proteins involved in repairing cells that are in the early stages of damage from high blood pressure and cholesterol. “By the time arteries are blocked, you already have a serious problem,” says Dr. Sibinga. His findings could lead to new therapies that would save many lives.
Meet the Proteins

Dr. Sibinga is especially interested in proteins that are potent helpers and healers of the smooth muscle cells in the blood vessel walls:

- **Fat1 cadherin.** Levels of Fat1 cadherin, found in cell membranes, increase significantly after vascular injury. The protein receives chemical signals from nearby cells injured by the chronic inflammation of atherosclerosis. It then controls the growth and movement of individual cells to orchestrate vascular repair.

- **Atrophins.** Levels of atrophin proteins also rise significantly after vascular injury. Atrophins bind to Fat1 cadherin to steer just the right number of newly made smooth muscle cells to weak or damaged areas of the vessel wall. Mouse studies show that when smooth muscle cells produce too little Fat1, the repair process goes haywire and too many smooth muscle cells are laid down in the injured area of the blood vessel wall—leading to a dangerous thickening.

- **Beta-catenin.** This protein, which also binds to Fat1, helps injured smooth muscle cells survive during repair by turning on specific survival genes that help the cells cope with vascular damage.

These proteins may be especially useful in treating restenosis and post-transplant arteriosclerosis.

Restenosis. Balloon angioplasty and stenting are used to widen coronary arteries narrowed by heart disease. But up to 40 percent of the time, these widened arteries re-narrow—a process known as restenosis. “Once we understand the signals by which Fat1 promotes migration of cells to the site of a vascular injury, it could lead to a new generation of stents coated with the protein, which will directly contact smooth muscle cells and speed the body’s natural healing process,” says Dr. Sibinga, also an attending physician in the division of cardiology at the Montefiore Einstein Center for Heart and Vascular Care. Mobilizing atrophins and beta-catenin also could help the repair effort.

**Post-transplant arteriosclerosis:** Within 10 years of receiving a heart transplant, about half of the patients experience thickening of the coronary artery walls. This artery thickening reduces blood supply to the heart and can lead to heart failure. We already know that Fat1 is turned on in transplant arteries as well as in other vascular injury settings and could be a potential therapy. Dr. Sibinga is studying another protein, colony stimulating factor 1 (CSF-1), which causes inflammation in blood vessel walls. In experiments, mice that can’t produce CSF-1 don’t develop transplant arteriosclerosis. This finding suggests a new prevention strategy in humans: several investigational cancer drugs that inhibit CSF-1 may also prevent transplant arteriosclerosis. (Less is known about atrophins’ and beta-catenin’s role in transplant arteriosclerosis.)

Meanwhile, when Dr. Sibinga counsels patients about heart health, he emphasizes the role of inflammation and the importance of taking statins. (See Q&A below.)

Journey to the Center of a Blood Vessel (continued from page 1)
Visualizing Success in Cardiac Revascularization

Mario J. Garcia, M.D.
Professor of Medicine (Cardiology)
Professor of Radiology
Pauline A. Levitt Chair in Medicine
Chief, Division of Cardiology
Albert Einstein College of Medicine
Co-director, Montefiore Einstein Center for Heart and Vascular Care

Heart failure results from the abnormal function of any portion of the heart. When the dysfunction occurs in the left ventricle, poor blood flow in the vessels that nourish it is often the cause. Restoring the blood supply is imperative—and cardiologists generally recommend invasive catheterization or surgical revascularization procedures.

Although revascularization is successful in many patients, its risks may outweigh its benefits in others. A new study led by Dr. Garcia and cardiology fellow Jorge Romero, M.D., found that certain imaging techniques work best in predicting whether a patient will respond well to these invasive treatments.

Their analysis, published in the May 2012 issue of JACC Cardiovascular Imaging, endorsed the imaging techniques known as contrast-delayed enhancement and low-dose dobutamine MRI. These methods enable physicians to see whether a patient’s heart can handle the invasive procedure and will respond well to it. Combining the two techniques can be particularly useful in predicting whether revascularization surgery will succeed.

Modulating the Immune Response

Nikolaos G. Frangogiannis, M.D.
Professor of Medicine (Cardiology)
Edmond J. Safra/Republic National Bank of New York Chair in Cardiovascular Medicine
Albert Einstein College of Medicine

If a region of the body is deprived of blood for long enough, the cells there will die. When this happens in heart muscle, the immune system launches a response that serves to heal the injury but, if prolonged or dysregulated, can also damage the heart, causing cardiac enlargement and, ultimately, heart failure. Mammals naturally express molecules that keep the immune system in check. A study led by Dr. Frangogiannis showed that IRAK-M, a molecule produced after injury as a “stop” signal that restrains the immune response, decreases cardiac damage after an acute infarction.

Dr. Frangogiannis and his team used genetic methods to ablate (remove) IRAK-M in mice and observed a more damaging response—and heart enlargement—after cardiac injury. Applied to humans, these results suggest that patients who have heart enlargement and develop heart failure after a heart attack may not properly activate signals that suppress inflammation. The researchers’ findings were published in a 2012 issue of Arteriosclerosis, Thrombosis, and Vascular Biology.

HIV and Atherosclerosis

Robert C. Kaplan, Ph.D.
Professor of Epidemiology & Population Health
Albert Einstein College of Medicine

HIV antiretroviral therapy has lengthened the lives of people infected with HIV—but survivors often go on to develop cardiovascular disease (CVD), setting the stage for heart attack and stroke.

Dr. Kaplan and his colleagues recently examined how well blood cholesterol levels in HIV-positive women predict their risk for atherosclerosis, which occurs when fatty substances are deposited in the arteries and can lead to CVD.

The researchers carried out ultrasound scans of the carotid arteries of the HIV-positive women to assess atherosclerosis severity, and they also measured the women’s blood cholesterol levels. Higher cholesterol levels were strongly associated with atherosclerosis severity among HIV-positive women on antiretroviral therapy. But the link was less clear for the HIV-positive women not receiving such therapy.

These results suggest that standard blood cholesterol levels may not be an adequate indicator of CVD risk in untreated HIV-infected women.

The study appeared in a 2012 issue of Atherosclerosis with Dr. Kaplan as senior author.

ON THE WEB

To learn more about the Wilf Family Cardiovascular Research Institute, please visit the institute’s website at www.einstein.yu.edu/centers/cardiovascular-research.

EASY AS ABC

Cardiovascular disease is the number-one cause of death in the United States, and stroke is number four. Avoiding them is as easy as ABC:

Avoid tobacco
Become more active
Choose good nutrition
NOTABLE GIFTS AND GRANTS

The Wilf Family Cardiovascular Research Institute gratefully acknowledges the generosity of the individuals and organizations whose support is critical to advancing our mission.

Congratulations!

Dr. Richard N. Kitsis, director of the Wilf Family Cardiovascular Research Institute and the Dr. Gerald and Myra Dorros Chair in Cardiovascular Disease, has received a Scholar Innovator Grant of $100,000 per year for two years from the Harrington Discovery Institute at University Hospitals Case Medical Center in Cleveland. The grant program supports the nation’s best physician-scientists in their efforts to accelerate promising drug discoveries into novel treatments for patients. In addition to the grant, the Scholar Innovators have access to a newly formed, world-class Innovation Support Center, where industry experts provide critical commercialization assistance and financial resources to help the discoveries progress into products.

Dr. Kitsis is in august company; nine other winners hail from such institutions as the University of Pennsylvania, Johns Hopkins University, Stanford University and the University of California, San Francisco. He was the only investigator to receive a grant for heart research.

Dr. Kitsis will direct the grant funds toward his joint effort with Evripidis Gavathiotis, Ph.D., assistant professor of biochemistry and of medicine, to create the first-in-class drug to reduce heart cell damage from acute myocardial infarction.

Dr. Kitsis is also a professor of medicine (cardiology) and of cell biology.

The International Society of Heart Research has selected Dr. Kitsis to deliver the 2013 President’s Distinguished Lecture at its world congress in July in San Diego.

Dr. Mario J. Garcia, a professor of medicine (cardiology) and of radiology and the Pauline A. Levitt Chair in Medicine, has received the 2012 Outstanding Dominican American in Medicine Award from the American Chamber of Commerce of the Dominican Republic. Luis Heredia Bonetti, founder of Dominican Week and past president of the American Chamber of Commerce of the Dominican Republic, presented the award to Dr. Garcia at a ceremony in Washington, DC, last fall. Dr. Garcia was honored for his contributions in advancing cardiovascular care through clinical excellence and research.

Dr. Garcia is also chief of the Einstein/Montefiore division of cardiology and co-director of the Montefiore Einstein Center for Heart and Vascular Care.